



DECLARATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Chun-Ying Huang Group: 1614

Serial No: 09/768,442

Examiner: Cook, Rebecca

Filed: January 24, 2001

For: Pharmaceutical Composition For The Treatment Of Hepatocellular Carcinoma

Attorney docket: U012951-1

Commissioner for Patents

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I, Stella Shihyi Shiue Chang, a citizen of the Republic of China (Taiwan), was graduated from National Taiwan University with a Bachelor's degree in Botany and from the Medical School, University of Arizona with PhD degree in Microbiology & Immunology. I also undertook postdoctoral training at the Institute of Molecular Biology, Academia Sinica, and served as the project manager of Biotechnology & Pharmaceutical Industries Program Office in the Ministry of Economic Affairs (MOEA). I am currently the project manager of R&D Department, TTY Biopharm Company Limited. I have read and understood the specification of US patent application 09/768,441.

It is known that many cancers are involved with angiogenesis and derived from epithelial cells. For instance, as mentioned in Tables 3 to 8 of Steven Brem, "Angiogenesis and Cancer Control: From Concept to Therapeutic Trial," (see Annex 1), angiogenesis is a phenomenon related to many cancers, including breast, lung (non-small cell), pancreas, malignant glioma, ovary, prostate, colon, acute leukemias, solid tumors, colorectal, renal, Kaposi's sarcoma, von Hippel-Lindau, leiomyosarcoma, brain, melanoma, and gastrointestinal cancers. Also as mentioned on the website, Department of Human Biological Chemistry & Genetics at The University of Texas

Medical Branch at Galveston (see Annex 2), colon cancer can result from progressive loss of regulation of the normal growth inhibitory, differentiation and apoptotic signals in colonic epithelial cells; and on the website, The Ovarian Cancer Forum of Med Help International (see Annex 3), the most common type of ovarian cancer is epithelial cancer - this type of cancer arises from the cells covering the surface of the ovary.

On the other hand, liver related cancers are mainly divided into two types: one is derived from hepatocytes and the other is metastasized from other tissues or organs. The former one is the so-called primary malignant hepatic tumors. Among others, hepatocellular carcinoma (hepatoma) is well known. In addition, liver related cancers also include the cancers derived from the tissues and cells in liver, such as hemangiosarcoma derived from blood vessels, hepatoblastoma derived from hepatogenic cells, and cholangiocarcinoma derived from the bile duct.

Given the above, it is understood that the mechanisms of the formation of cancers, including liver related cancers, are quite diverse.

So thus far, it appears that no medicine is expected to be effective in treating all types of cancers. For instance, Navelbine® (see Annex 4), has received an approval in two specific cancers, i.e., non-small lung cancer and breast cancer (which is a type of epithelial cell associated cancer). However, Navelbine® is **not** effective in combating all types of cancers, particularly hepatocellular carcinoma. Instead, Navelbine® has adverse effects on hepatic organ sites. Furthermore, doxorubicin is helpful for treating brain cancers, which is recognized as an angiogenic cancer as mentioned above. Furthermore, as reported in the results of the delivery of doxorubicin (Adriamycin) to the brain for treatment of tumors (see Annex 5), and the study on brain tumour drug delivery (see Annex 6), doxorubicin is an effective chemotherapeutic drug for breast cancer and since 17% of all breast cancer patients experience metastases to the brain, doxorubicin could be potentially useful in the treatment of these tumors. However, a patient suffered from brain tumors while having developed liver disease, could not take an effective dose to treat the former cancer, simply because of undesirable side effects (see Annex 7). The above two examples clearly elucidate that anti-cancer drugs are effective in some specific cancers only, but not effective in other types of cancers, particularly hepatocellular carcinoma.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Signed this *24th* day of *Oct.*, 2003

By *Stella S. S. Chang*
Stella Shihyi Shiue Chang